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| (51) International Patent Classification ⁶ : C07D 211/26, A61K 31/445 | A1 | (11) International Publication Number: WO 98/38165 (43) International Publication Date: 3 September 1998 (03.09.98) |
| (21) International Application Number: PCT/US98/01304 (22) International Filing Date: 23 January 1998 (23.01.98) (30) Priority Data: 08/810,503 28 February 1997 (28.02.97) US (71)(72) Applicant and Inventor: AMER, Moh, Samir [US/US]; 877 Sandpoint Road, Carpinteria, CA 93013 (US). (74) Agents: RICHARDS, John; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al. | | (81) Designated States: AU, CA, FI, JP, KR, NO, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>With amended claims.</i> |
| (54) Title: S-2'-(2-(1-METHYL-2-PIPERIDYL) ETHYL) CINNAMANILIDE AS A 5-HT ₂ RECEPTOR ANTAGONIST (57) Abstract The 5HT ₂ receptor antagonizing effect of 2'-[2-(1-methyl-2-piperidyl) ethyl] cinnamanilide, a racemic mixture (R S-MPEC) of S-MPEC and R-MPEC isomers is found to be provided practically entirely by the S-MPEC isomer, the R-MPEC being effectively an impurity. Disclosed are pure S-MPEC, mixtures thereof with up to about 10 % of R-MPEC, a novel method of resolving the S-MPEC involving a novel intermediate compound, therapeutic compositions containing S-MPEC, and uses thereof for administration to animals, especially humans, in need of 5HT ₂ receptor blockage, as for hemorrhoids, varicose veins, venous and coronary insufficiencies, wound healing, and as analgesic or local anesthetic agents. | | |

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S-2'-(2-(1-METHYL-2-PIPERIDYL) ETHYL) CINNAMANILIDE AS A 5-HT₂ RECEPTOR ANTAGONIST

This invention relates to a specific isomer, namely a specific S (or (-) or 1 or levo) isomer, in particular the compound S-2'- [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide or its acid salt, its preparation and its use in therapeutic treatments and compositions as a 5-HT₂ receptor antagonist (blocker) for treating or preventing hemorrhoids, varicose veins, or venous or coronary insufficiency, treating wounds or as analgesic or local anesthetic agents in animals including mammals, especially humans.

In my U.S. Patent No. 5,266,571 dated November 30, 1993, the entire disclosure of which is incorporated herein by reference thereto, I have disclosed and claimed a method for treating or preventing hemorrhoids in animals by administration of a 5-HT₂ receptor antagonist based on the discovery that 5-HT (5-hydroxytryptamine or serotonin) plays an important role in mediating both the increase in venous pressure and/or platelet clumping that lead to the congestion of the veins in the hemorrhoidal plexus, that 5-HT₂ receptors rather than 5-HT₁ receptors are involved, and that 5-HT₂ receptor antagonists thus inhibit hemorrhoids. As such preferred antagonists are mentioned 2'- [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide hydrochloride (MPEC) and two other compounds.

In my U.S. Patent 5,605,902 dated February 25, 1997, the entire disclosure of which is herein incorporated by reference thereto, and of which the present application is a continuation-in-part, which prior U.S. application corresponds to PCT WO94/18958 published September 1, 1994, I further disclose and claim the use of the same 5-HT₂ receptor antagonists for treating or preventing varicose veins or venous insufficiency or for treating wounds.

OBJECTS OF THE INVENTION

It is an object of this invention to provide a new and improved form or species of 5-HT₂ receptor antagonist, a new intermediate compound for making such antagonist, methods and means for preparing such intermediate and antagonist, and use of such antagonist in therapeutic treatments and compositions.

Another object of this invention is to provide a new, improved, purer, unadulterated and/or more effective form of MPEC for use in such treatments and compositions.

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Other objects and advantages will appear as the description proceeds.

SUMMARY OF THE INVENTION

In accordance with certain of its aspects, the attainment of one or more of the foregoing objects is made possible by this invention which comprises separating the racemic (RS) MPEC mixture employed in the inventions of my said
5 two prior U.S. applications into its individual S and R(or (+) or d) isomers and discovering that the R isomer is totally or substantially devoid of any activity as a 5-HT₂ receptor antagonist and is in that respect an adulterant or impurity in any mixture with the S isomer, in which mixture the S isomer is the only active 5-HT₂
10 receptor antagonist, and that the S isomer (S-MPEC) is thus unexpectedly at least twice as effective as a 5-HT₂ receptor antagonist as the racemic MPEC mixture (RS-MPEC). Thus, the 5-HT₂ receptor blocking effect achieved with any given amount of the RS-MPEC can be achieved with say half that amount of the S-MPEC. Other disadvantages would be inherent in any therapeutic composition containing an equal
15 amount of active ingredient and adulterant. The isomeric and racemic forms of MPEC have in common the empirical formula C₂₃H₂₈N₂O, (M.W. 348.49).

DETAILED DESCRIPTION OF THE INVENTION

This invention comprises the provision, use in therapeutic compositions and in treatment of animals in need of a 5-HT₂ receptor blocking
20 effect, of compounds or mixtures thereof selected from the group consisting of R isomer-free S-2'- [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide (S-MPEC), a pharmaceutically acceptable acid salt thereof, and any mixtures thereof with up to about 10% of any of their corresponding R-isomers (R-MPEC) and salts thereof.

The aforesaid mixtures preferably contain no more than about 4%,
25 more preferably no more than about 1%, of the R-MPEC impurity, the S-MPEC is preferably the hydrochloride salt, and/or the S-MPEC is preferably devoid of R-MPEC. The term "substantially free of the R isomer" (or equivalent) is intended to cover mixtures containing from about 0.0001% to about 10% of the R isomer (stereoisomer).

30 The invention also comprises the production of a novel intermediate, S-[2-(o-aminophenethyl)-1-methyl piperidine-dibenzoyl-L-tartrate salt] (S-APEMP.DBLT (or.L-DBT)) comprising reacting 1 mol of 2-nitrobenzaldehyde with

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1 mol of 2-picoline in the presence of acetic anhydride and treating the resulting 2-(o-nitrostyryl)-pyridine with a quartermizing methylating agent to produce the corresponding 2-(o-nitrostyryl)-1-methylpyridinium (NSMP) salt, reducing the pyridinium salt by catalytic hydrogenation to produce the corresponding RS-2-
5 (o-aminophenethyl)-1-methylpiperidine (RS-APEMP) hydro salt, treating the hydro salt with an alkaline agent to liberate the free base (RS-APEMP) and treating the free base with dibenzoyl-L-tartaric acid (DBLT or L-DBT) to produce the novel S-APEMP-DBLT. The latter is then treated with an alkaline agent to liberate the free base (S-APEMP) which is then reacted with an equimolar amount of cinnamoyl
10 chloride to produce S-MPEC.

In the above process, the initial steps for producing the NSMP salt are disclosed in Dykstra et al, J. Med. Chem 16 1015 (1973) and L. Horwitz, J. Org. Chem. 21 1039 (1956), and the next step of producing APEMP hydro salt is disclosed in Dykstra, et al, U.S. Patent No. 4,064,254, especially EXAMPLE 1.
15 EXAMPLES 1, 25 and 141 of the latter patent disclose the production of the "l"-MPEC and "d"-MPEC separately using procedures quite similar to applicant's above-described process except that the separation is achieved with d-camphoric acid in 95% ethanol (instead of applicant's dibenzoyl-L-tartaric acid) and requires fractional crystallization which is inefficient. Also, the -42.8° optical rotation
20 reported in the patent for the "l"-MPEC indicates a reduced efficiency (compared with applicant's S-MPEC product with a -46° optical rotation).

It is further significant that this '254 patent discloses no recognition of any possibility that the properties of the S and R isomers of MPEC might differ, much less that one isomer might be completely inactive in a field in which the other
25 isomer is highly active, much less when that activity is for blocking 5-HT₂ receptors, much less for treating or preventing hemorrhoids, varicose veins or venous or coronary insufficiency or treating wounds or as analgesic or local anesthetic agents. Applicant's U.S. Patent No. 5,266,571 discussed the insufficiency of prior art suggesting antiserotonin activity broadly as a basis for urging
30 anticipation of an invention based on 5-HT₂ receptor antagonism. A similar situation exists here, the only activity disclosed in the '254 patent being antiarrhythmia and antiserotonin.

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The S-MPEC (or its salt) in pure form or containing the slight indicated amounts of the inactive R isomer impurity, may be provided and used in free form or in or with a non-toxic pharmaceutically acceptable solid, liquid or particulate carrier in the form of a paste, ointment, cream or gel composition
5 suitable for topical or rectal administration, desirably with a gelling, binding or thickening agent to provide the desired viscosity, or in the form of a tablet, capsule, chewing gum, lozenge, powder, spray, aerosol, enema, suppository, syrup, elixir, aqueous or oily suspension, emulsion or solution, paste, ointment, cream or gel suitable for systemic oral, rectal or parenteral administration as by subcutaneous,
10 intraperitoneal, intramuscular or intravenous injection or by transdermal or inhalation therapy.

The S-MPEC may be employed in free form or as a generally water soluble non-toxic pharmaceutically acceptable acid addition salt with such relatively non-toxic organic or inorganic acids as sulfuric, sulfonic, phosphoric, phosphonic,
15 hydrobromic, hydrochloric, hydriodic, sulfamic, methanesulfonic, benzenesulfonic, para-toluenesulfonic, acetic, lactic, succinic, malic, mucic, tartaric, citric, gluconic, benzoic, cinnamic, isethionic and the like.

Suitably the compositions of this invention comprise sufficient active S-MPEC material to provide a dose of from 0.05-10 mg. per kg. of body weight,
20 more suitably 0.2-6 mg/kg body weight. These compositions may be taken 1-3 times daily or as needed until the symptom or condition being treated subsides or is corrected.

The compositions of this invention may contain the active ingredient in amounts ranging from less than 1% to over 99%, with any remainder being a
25 pharmaceutically acceptable solid or liquid carrier, which may contain other conventional excipients. Examples of such carriers and excipients include fillers, binders, flavors, sweeteners, bulking and coloring agents, antioxidants, anionic, nonionic, cationic, zwitterionic, and amphoteric surface active detergents, sudsing, dispersing and emulsifying agents, buffering and pH adjusting agents, water and
30 organic solvents, humectants, thickeners, preservatives, stabilizers, mold release agents, disintegrants, anti-disintegrants, lubricants and the like. Examples of conventional pharmaceutically acceptable carriers and excipients are profusely

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conventional pharmaceutically acceptable carriers and excipients are profusely disclosed in the prior art including discussions in U.S. Pat. No. 4,515,772 (Parran et al, Proctor & Gamble), U.S. Pat. No. 4,966,777 (Gaffar et al, Colgate-Palmolive Company), and U.S. Pat. No. 4,728,512 (Mehta et al, American Home Products),

5 which discussions are incorporated herein by reference thereto.

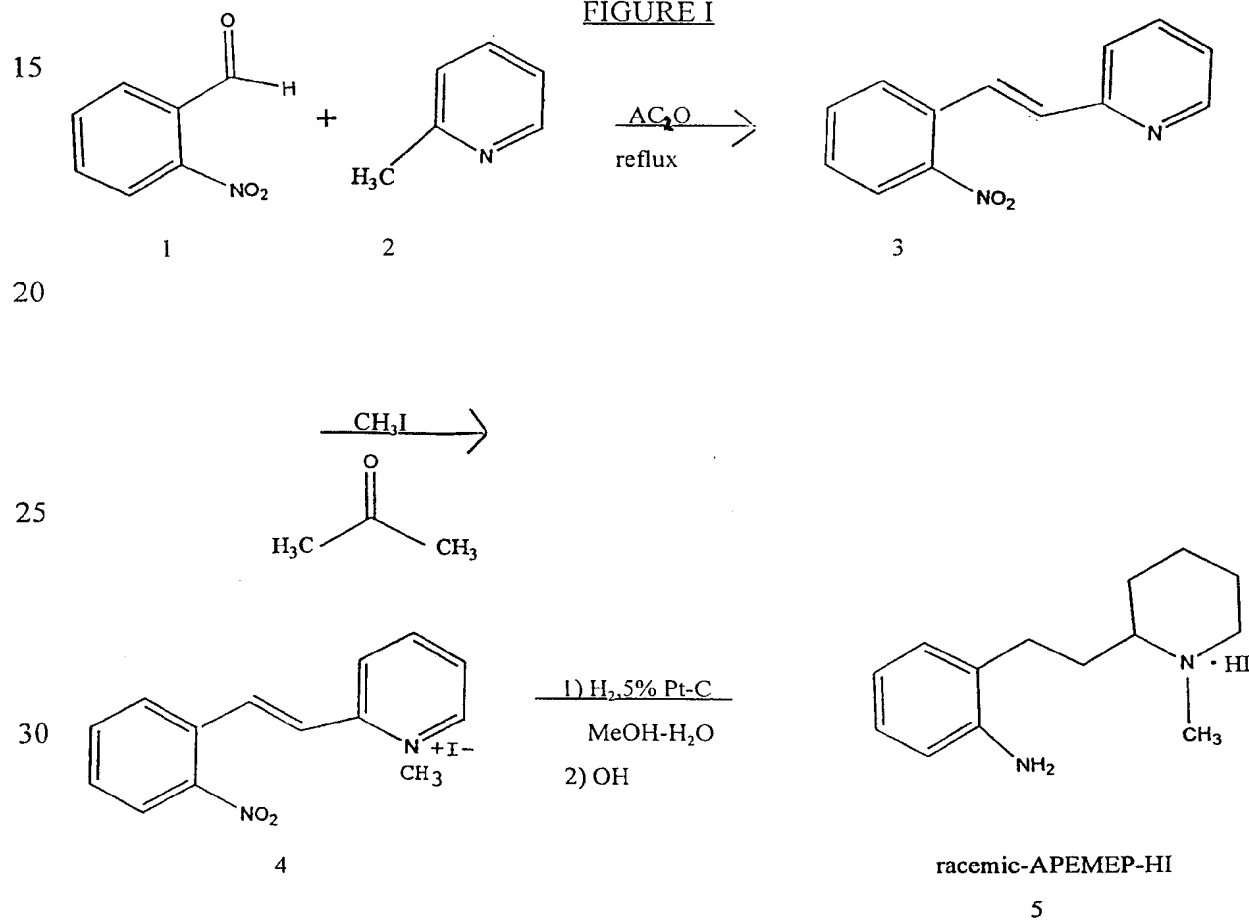
The following examples are only illustrative of certain preferred embodiments of this invention. All parts and proportions referred to herein and in the appended claims are by weight and temperatures are in degrees Centigrade, unless otherwise indicated.

10 Example 1 below illustrates by equation and description one preferred embodiment of a method of making S-MPEC, with supporting data characterizing, identifying and/or corroborating the properties of intermediates, final products, etc.

Example I

PREPARATION AND CONFIRMATION OF S-MPEC

FIGURE I

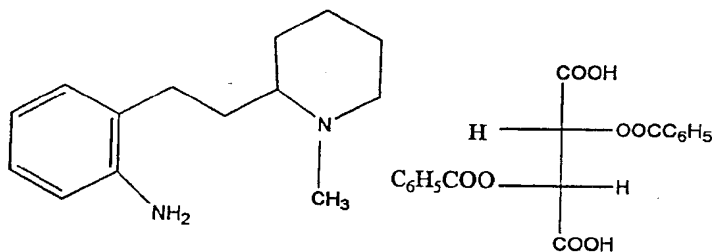


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$\xrightarrow{\text{NaOH / EtOAc}}$
Dibenzoyl-L-tartaric
acid, MeOH

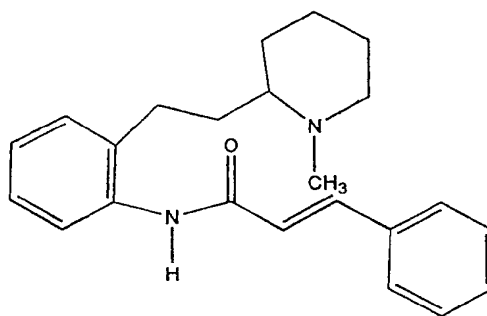


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20

$\xrightarrow{\text{Na}_2\text{CO}_3 / \text{EtOAc}}$
 $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCl}$
 $\text{K}_2\text{CO}_3 / \text{EtOAc}$



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1. 2 - nitrobenzaldehyde
2. 2 - picoline
3. 2 - (o-nitrostyryl) pyridine (NSP)
4. 2 - (o-nitrostyryl)-1-methylpyridinium iodide
- 5 5. RS-2- (o-aminophenethyl)-1-methylpiperidine. HI
6. S-[2-(o-aminophenethyl)-1-methylpiperidine-dibenzoyl-L-tartrate]
(S-APEMP. DBLT OR .L-DBT)
7. S-2'- [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide (S-MPEC)
- 7a. Cinnamoyl chloride

10 S-MPEC CHEMICAL PROCESS

(A) 2-(o-Nitrostyryl) -1-Methylpyridinium Iodide (NSMP-I)

To a 50 L round bottomed flask was added 2-nitrobenzaldehyde (3,500 g. 23.2 moles), 2-picoline (3.2L., 32.8 moles) and acetic anhydride. The mixture was stirred efficiently under an inert atmosphere (nitrogen or another inert gas) and heated to reflux for 27 hrs. The mixture was cooled to under 100 C., for safe handling, and quenched in a suitable vessel equipped with external cooling and efficient stirring on 10.5 Kg. of ice. The pH was adjusted to 11 with 45% aqueous sodium hydroxide at a rate to keep the temperature below 50°C. After cooling to 20-30°C., the granular solid was collected by filtration, washed well with water.

Yield 6572 g. of crude 2-(o-nitrostyryl) pyridine (NSP).

This solid was transferred to a 50L, round bottomed flask, dissolved in acetone (14L.) and iodomethane (2.94L., 47.7 moles) (quaternizing methylating agent) was added. (Other such (alkylating) agents may be used, generally having the formula CH_3X , X being an anion such as sulfate, methyl sulfate, halide (Cl, Br, I), etc.). The mixture was heated to reflux under an inert atmosphere (nitrogen or another inert gas) for 18 hrs. After cooling to 20°C. the precipitate was collected by filtration and washed with acetone or a 1:1 mixture of acetone:ethyl acetate (3x3.5L.). Drying to constant weight at 50-60°C. yielded 6,839 g. (80%) of NSMP.I.

30 (B) RS- 2-(o-Aminophenethyl)-1-Methylpiperidine. Hydroiodide (RS-APEMP.HI)

In a 5 gallon reactor, a solution of NSNP.I (935 g., 2.5 moles) in

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methanol (14L.) was reduced in a hydrogen atmosphere (Psi. 55) in the presence of Pt/C (5 or 10%, 98g.). After removal of the catalyst and evaporation of the filtrate in the usual manner, the residue was dissolved in hot methanol (2.8L.). Ethyl acetate (2.8L) was added to the hot mixture to induce crystallization, yield 516.3 g. (59%) of RS-APEMP.HI.

(C) S-[2-(o-Aminophenethyl)-1-Methylpiperidine Dibenzoyle-L-Tartrate] (S-APEMP.DBLT)

A solution of RS-APEMP.HI (516g., 1.5 mole) ethyl acetate (5.5g.) (or other low boiling water immiscible solvent such as benzene, toluene etc.) was extracted with 5% aqueous sodium hydroxide to liberate the free base (organic phase), washing the organic phase with water, drying over a suitable drying agent (such as anhydr. sodium sulfate, magnesium sulfate, potassium carbonate etc.) After separating the solvent from the drying agent the solution was evaporated in vacuo and the residual RS-APEMP free base was dissolved in methanol (1.0L.) and a solution of dibenzoyl-L-tartaric acid (540 g., 1.5 moles) in methanol (2.3 L.) was added. The mixture was held overnight at room temperature. The crystalline precipitate was collected and recrystallized from methanol (3.4 L.), yield 246g. of S-APEMP.DBLT. (28.6%, wt; 57.2% of the S-APEMP).

(D) S-2'-[2-(1-Methyl-2-Piperidyl)ethyl] Cinnamanilide (S-MPEC)

A solution of S-APEMP.DBLT (287 g, 0.5 mole) in ethyl acetate (3.2 L.) (or other low boiling water immiscible solvent) was extracted with 7.5% aqueous sodium bicarbonate (3.2 L.) to liberate the S-APEMP. After a water wash and drying over a suitable drying agent the solvent was removed in vacuo. The oily residue, S-APEMP, was dissolved in ethyl acetate (1.0 L.) and anhydrous potassium carbonate (412 g, 3.0 moles) (or other suitable acid acceptor such as triethyl amine, pyridine etc.) was added. Cinnamoyl chloride (143 g., 0.7 mole) in 700 ml. of ethyl acetate was added slowly. After the initial reaction, the mixture was refluxed for 14 hrs. After cooling to room temperature the mixture was extracted with water (1.7 L.) and dried over a suitable drying agent. After removing the drying agent the solvent was removed in vacuo and the residue was dissolved in hot ethyl acetate (280 ml.) and allowed to slowly cool to room temperature; filtration yielded S-MPEC, (136 g., 79% yield). Analysis: Calcd. For C, H, N : C, 79.27; H, 8.10;

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N, 8.04. Found: C, 79.27; H, 8.06; N, 8.07. HPLC(chiral)purity: 99.5%, $[\alpha]_{D25} = -46^\circ$ (c=0.01, EtOH); Melting point: 128°C.

Absolute Configuration of l-MPEC

Summary

5 Absolute configuration of l-MPEC was determined to be S by X-ray crystallography of l-APEMP · L-DBT · 2H₂O, which is an intermediate of l-MPEC.

Since elaboration to grow crystals of l-MPEC did not yield any successful results, recrystallization of fine crystals of l-APEMP · L-DBT, which is
10 an intermediate of l-MPEC, was then tried. Slow recrystallization of l-APEMP · L-DBT gave large enough crystals of corresponding dihydrate.

Recrystallization

l-APEMP · L-DBT----->l-APEMP · L-DBT · 2H₂O

MeOH-water (1/1)

15 Absolute configuration of l-APEMP · L-DBT · 2H₂O was determined to be S by X-ray crystallography. Configuration of l-APEMP · L-DBT is retained under reaction conditions of which conversion to l-MPEC shown in Fig. 1, because cinnamoyl chloride reacts only with amino group on the benzene ring, and does not affect any other part of the molecule. Consequently, absolute configuration of l-
20 MPEC was determined to be S.

Experimental

500 mg of fine crystals of l-APEMP · L-DBT, of which stereo-chemical purity was > 99.5% d.e., was dissolved in 10 mL of methanol/water (1/1) and the crystals were grown up for 7 days at room temperature, to give crystals of
25 l-APEMP · L-DBT · 2H₂O. Experimental details and results of the X-ray crystallography are summarized in Table 1.

The equipments used for the X-ray crystal structure analysis of the l-APEMP-L-DBT salt were as follows:

| | |
|------------------------|--|
| Measuring device: | ENRAF NONIUS CAD4 (an automatic X-ray diffractometer for single crystal) |
| Measuring software: | Express® |
| Computer for analysis: | DEC VAX3100 |
| Software for analysis: | Molen® |

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TABLE 1

X-ray crystallography of *l*-ADEMP-L-DBT · 2H₂O

| | | |
|----|-------------------------------|---|
| | Sample Name | : <i>l</i> -ADEMP · L-DBT · 2H ₂ O |
| | Molecular Formulas | : C ₃₂ H ₃₆ N ₂ O ₈ · 2H ₂ O |
| 5 | X-rays | : CuK α (λ = 1.54184 Å) |
| | Crystal Size (mm) | : 0.4 X 0.3 X 0.3 |
| | Crystal System | : Orthorhombic |
| | Space Group | : P2 ₁ 2 ₁ 2 ₁ |
| | a (Å) | : 13.3583 (7) |
| 10 | b (Å) | : 30.298 (2) |
| | c (Å) | : 7.8105 (6) |
| | vol. (Å ³) | : 3161.2 (5) |
| | z | : 4 |
| | 2θ (deg.) | : 6.4 < 2θ < 150 |
| 15 | D (calcd.) | : 1.287 |
| | R* | : 0.052 |
| | Number of Reflections | : 3724 |
| | Number of Parameter used | : 518 |
| | μ (CuK α) (cm ⁻¹) | : 1.89 |
| 20 | Number of I > 3 σ (I) | : 3476 |
| | Maximum e/Å ³ | : 0.239 |
| | Standard Reflection | : 24 points (8 < θ < 14) |
| | Data Correction Method | : Lorentz and Polarization Effect |
| | Reflection Data Collection | : Enraf Nonius CAD-4 System |
| 25 | Structure Determination | : Enraf Nonius MolEN Program |

$$* R = (\sum |F_0| - \sum |F_e|) / \sum |F_0|$$

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TABLE 2

CERTIFICATE OF ANALYSIS

Compound Name: (-)-2'-[2-(1-Methyl-2 piperidyl)ethyl]cinnamanilide(*l*-MPEC,S-MPEC

| 5 | <u>TEST</u> | <u>SPECIFICATION</u> | <u>RESULTS</u> |
|----|--|--|---|
| | Physical Description | White to off-white solid with no visible contaminants | White to off-white solid with no visible contaminants |
| | ¹ H NMR (CDCl ₃) 300 MHz | Conforms to Spectrum # B3-13055 | Spectrum # B3-16514 conforms to Spectrum # B3-13055 |
| 10 | FTIR (Neat, Acetone) | Conforms to Spectrum # FTO155 | Spectrum # FT0712 conforms to Spectrum # FTO155 |
| | R.O.I | ≤ 0.1% | 0% |
| | Melting Point | Record | 128°C. |
| | HPLC (Chemical) | Chemical Purity ≥ 98% with no single impurity over 0.5 % | Same |
| | HPLC (Chiral) | Chiral Purity ≥ 99.5 % | > 99.5 % |
| 15 | GC (Residual solvents) | Acetone ≤ 0.2% Ethyl Acetate ≤ 0.2% Methanol ≤ 0.2% Hexane ≤ 0.2% | < 0.1 % = 0.13 % < 0.1 % < 0.1 % |
| | Water Content (Karl Fisher) | ≤ 5.0 % | 0.2 % |
| | Heavy Metals | ≤ 0.005 % | < 0.005 % |
| 20 | Optical Rotation (EtOH) | Record | -46° |
| | Elemental Analysis | C 79.27 ± 0.4 H 8.10 ± 0.4 N 8.04 ± 0.4 | 79.27 8.06 8.07 |

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TABLE 3

CERTIFICATE OF ANALYSIS

Compound Name: d-2'-[2-(1-Methyl-2-piperidyl)ethyl]cinnamanilide (R-MPEC, (+)-MPEC)

| 5 | <u>TEST</u> | <u>RESULTS</u> |
|----|---|--|
| | Physical Description | White solid, with no visible contaminants |
| | ¹ H NMR (CDCl ₃) 300MHz | Spectrum #B3-16942 conforms to structure |
| | FTIR(Neat, Acetone) | Spectrum #FTO798 conforms to structure |
| 10 | MP | 128°C. |
| | Elemental Analysis | C = 79.19 % H = 8.09 % N = 8.03 % |
| | HPLC (Chemical) | 99.8 % with no single impurity > 0.5 % |
| 15 | HPLC (Chiral) | 99.9 % |
| | R.O.I | < 0.1 % |
| | GC (Residual solvents) | Acetone < 0.2% Ethyl Acetate = 0.3 % Methanol < 0.2 % Hexane < 0.2 % Ethanol < 0.2 % |
| 20 | Water Content (Karl Fischer) | 0.4 % |
| | Heavy Metals | < 0.005 % |
| | <u>Additional Testing</u> | + 41° |
| 25 | Optical Rotation (c=0.01, Et(OH) | |

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EXAMPLE 2

Effects of MPEC in Isolated Human Colon Vein Contracted with 5-hydroxy-tryptamine (5-HT)

The aim of this study was to determine the $1C_{50}$ of MPEC in isolated human colon vein contracted by 5-hydroxytryptamine. MPEC was tested under three forms: the racemate, the R-isomer and the S-isomer in order to identify the active isomer. Stock solutions of MPEC ($10^{-2}M$) (racemate, R and S-isomers) were prepared in acidified water (water - hydrochloric acid, 99.50 - 0.50%) and subsequently diluted in water.

5-HT (5-hydroxytryptamine or serotonin) was dissolved in water at $10^{-2}M$ and subsequently diluted in water.

Water used in this study was obtained from a Milli Q apparatus (Millipore).

Human colon veins were obtained from patients (4 males and 2 females, 60 ± 7 years old) undergoing resection of a part of the colon because of colon malignancy or polyposis. Immediately after surgical removal, a colon vein specimen was taken and immediately transported to the laboratory in physiological aqueous saline solution of the following composition (in mM): NaCl (112), KCl (5), $NaHCO_3$ (25) glucose (11.5), KH_2PO_4 (1.2), $CaCl_2$ (2.5) and $MgSO_4$ (1.2), pH 7.4. This solution was maintained at $37^\circ C$. (portable thermostated box, Veba Meditemp) and gassed with oxygen. Under stereo microscope, rings of the human colon veins (3-5 mm, 9.6 ± 1.1 mg, $n = 25$) without fat were prepared and mounted, under 500 mg. of resting tension, in a 25 mL organ bath containing physiological saline solution maintained at $37^\circ C$. (low-temperature thermostat Lauda RCS6) and gassed with 95% O_2 and 5% CO_2 . Tension was measured isometrically with a transducer (Grass FT 03) connected to an amplifier (bridge coupler type 570, Hugo Sach Electronic) coupled to an oscillographic recorder (Graphtec linearecorder mark VII WR 3101, Hugo Sach Elektronik) and a computer for data acquisition and control of electrovalves (Amstrad PC 1512SD equipped with AD/DA card and IO card).

Each ring was allowed to equilibrate for 60 min. in physiological saline solution. After this period, the human colon vein was stimulated by 5-HT ($3 \cdot 10^{-6} M$, concentration inducing a sub-maximal phasic contraction). When the

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maximal tension was observed, the colon vein was washed with physiological saline solution every 10 min. for 40 min. Once reproducible control contractions had been obtained, the preparations were incubated for 60 min. with MPEC (the racemate form, the S- or the R-isomer) at one fixed concentration: 10^{-9} , $3 \cdot 10^{-9}$ or 10^{-8} M or
 5 with water as control before a last contraction induction by 5-HT $3 \cdot 10^{-6}$ M. Only preparations in which the control contractions were matched were used. Preparations developing a tension lower than 250 mg. or weighing less than 2 mg. were discarded. No statistical difference of the control parameters values was observed between the different experimental groups.

10 The observed inhibition induced by MPEC was expressed as percentage of the last control contraction. The pD'_2 (the negative logarithm of the molar concentration of an antagonist capable of reducing to 50% the maximal response caused by an agonist) was calculated by the method of Van Rossum (1963). Only data relating to concentration of inhibitor which produced a mean
 15 inhibition between 10 and 90% were used. IC_{50} was calculated as the antilogarithm of pD'_2 .

Results were expressed as means \pm standard error of mean. Comparison between two means was made using the Student t test after checking variance homogeneity by X^2 test. Comparison among different means was made
 20 using an F test (variance analysis with one classification parameter) after checking homogeneity of the variances using Bartlett's test (Lambert, 1963).

TABLE 4

| | RS-MPEC | S-MPEC | R-MPEC | Selectivity* | Signification |
|---------|---------|--------|--------|--------------|---------------|
| pD'_2 | 8.35 | 8.77 | 7.23 | 34.67 | $P < 0.001$ |

25

* selectivity calculated as the antilog of the difference between the two pD'_2 values ((Furchgott, 1972). So, MPEC present a stereoselective activity.

The above results indicate that S-MPEC is 34.67 times as active as R-MPEC (twice as active as RS-MPEC) in blocking 5-HT₂ receptors in human
 30 colon veins. This is the principal mechanism of the activity of MPEC against hemorrhoids, varicose veins, venous and coronary insufficiency, wound healing and

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other 5HT₂ receptor-induced symptoms. R-MPEC is here shown to be essentially inactive and effectively an impurity.

EXAMPLE 3

Effects of MPEC on Phenylquinone-Induced Writhing in Mice

5 Mice dosed orally with certain analgesics, tranquilizers or anxiolytics do not respond in a typical manner to an intraperitoneal dose (2.5 mg/kg) of phenyl-p-benzoquinone (PPB). The usual response is writhing, characterized by stretching and twisting of the body. Blockade of this response is measured by comparing the number of writhing episodes observed at different dose levels of the test compound
10 with those observed in vehicle control animals. The writhing episodes for five animals are counted simultaneously with a 5-key laboratory counter. The total number of writhing episodes are counted for each mouse for exactly 10 min. after PPB injection.

Results of testing RS-, R-, and S-MPEC in the above procedure with
15 a saline control and a known analgesic Indomethacin are shown in the following table:

Table 5

| | Dose (mg/kg) | N | No. of Writhing |
|-----------------|--------------|----|-----------------|
| Saline | | 10 | 21.4±4.6 |
| 20 Indomethacin | 5 | 9 | 12.8±3.5 |
| RS-MPEC | 2.5 | 9 | 15.3±4.1 |
| R-MPEC | 2.5 | 9 | 25.3±4.2 |
| S-MPEC | 2.5 | 9 | 11.4±3.2 |

25 The above results show that R-MPEC permitting 25.3 writhings is substantially inactive as an analgesic, and S-MPEC permitting only 11.4 writhings provides substantially all the analgesic activity of the mixture of S-MPEC and R-MPEC in RS MPEC permitting 15.3 writhings. The surprisingly high analgesic activity of S-MPEC is an important property in the treatment of hemorrhoids,

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wounds and varicose veins and also useful often in treating venous and coronary insufficiencies.

EXAMPLE 4

Blockage of 5-HT₂ Receptors on Rat Forebrain.

5 Rats were sacrificed by decapitation to remove the cerebral cortex, to which a 10-fold volume of 0.32 M sucrose solution was added for homogenization with POLYTRON (setting: 6 and 30 seconds, KINEMATICA AG, Switzerland). Subsequently 10-minute centrifugation was conducted at 1,000 X G. The resulting supernatant was subjected to 20-minute centrifugation at 35,000 X G, and a 10-fold
10 volume of 50 mM Tris buffer (pH: 7.4; 25°C.) was added to the precipitate obtained before conducting resuspension. This suspension was subjected to 10-minute incubation at 37°C. before conducting 20-minute recentrifugation at 35,000 X G. The final precipitate was suspended in a 40-fold volume of buffer for measurement (50 mM Tris, 4 mM CaCl₂, 10 μM pargyline, 0.1% ascorbic acid, pH: 7.7, 25°C.),
15 and this suspension was used as the membrane preparation in the binding experiment. ³H-Ketanserine 0.1 ml. (Final concentration: 0.4 nM) and 0.4 ml. of the membrane preparation were added to the test drug (S-MPEC and R-MPEC) and to 0.5 ml. of buffer for measurement in which final concentration (1 μM) of methysergide was dissolved. The solution was prepared to make the total volume of
20 1.0 ml. and was allowed to react at 37°C. for 20 minutes. Following the completion of the reaction, the reactive solution was filtered by aspiration under reduced pressure using the 0.1% polyethyleneimine solution-impregnated Whatmann GF/C filter, and the filter was washed three times with 5 ml. of 50 mM Tris buffer (pH: 7.4, 25°C.) which was immediately cooled with ice, to which 5 ml. of scintisol
25 was added to measure the radioactivity on the filter with a liquid scintillation counter. The specific binding volume was determined to be the value obtained after deduction of the nonspecific binding volume under the presence of 1 μM methysergide from the total binding volume. All the experiment was conducted on a triplication basis. Protein assay of the membrane preparation used was conducted
30 according to the method of Lowry et al.

Results of testing S-MPEC and R-MPEC in the above procedure are shown in the following table:

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Table 6

| | S-MPEC | R-MPEC |
|-----------------------|--------|--------|
| IC ₅₀ (MM) | 1.73 | 116 |

- 5 The above results show that S-MPEC is 67 times (116/1.73) as potent as R-MPEC in blocking 5-HT₂ receptors from rat forebrains.

EXAMPLE 5

Effect of MPEC on serotonin plus collagen-induced pulmonary thromboembolic death in mice.

10 Purpose:

Serotonin plays an important role in thrombus formation. The antiserotonergic activity of MPEC is investigated through an inhibition of thromboembolic death.

Animals:

- 15 Male ddY strain mice

Reference drug:

Ticlopidine, clinically used as an antithrombotic.

Test drugs: S-MPEC, R-MPEC

Method:

- 20 Mice are used after overnight fasting. Acute pulmonary thromboembolism is induced by a rapid injection of the mixture serotonin (50 ug/10g b.w.) and collagen (10ug/10g b.w.) into the tail vein and then the mortality of mice within 10 min. is determined. Drugs are administered intra-rectally 1 hr. or orally 3 hr. prior to injection of serotonin and collagen. For oral administration the drug is
- 25 suspended in Tween 80/distilled H₂O (0.5% vol./vol.), and for intra-rectal dispersed in white petrolatum.

In this thrombosis model we selected the dose of each stimulus to produce 0 ~15% mortality by each stimulus alone and about 80% mortality by combination of both stimuli.

- 30 Test results are tabulated as follows:

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Table 7

| | Dose mg/kg | Route | % Protection (% alive mice) |
|-------------|------------|-------------|--------------------------------|
| Control | | | 0 |
| Ticlopidine | 100 | Oral | 78 |
| S-MPEC | 1 | Oral | 40 |
| S-MPEC | 3 | Oral | 50 |
| S-MPEC | 10 | Oral | 80 |
| S-MPEC | 2.5 | Intrarectal | 60 |
| S-MPEC | 5 | Intrarectal | 90 |
| S-MPEC | 10 | Intrarectal | 90 |
| R-MPEC | 10 | Oral | 25 |

These results suggest that MPEC may be absorbed through the intestine and exert antithrombotic effect. At an oral dose of 10 mg. per kg. of body weight, S-MPEC at 80% protection provides more than triple the 25% protection of R-MPEC. The anti-thrombotic activity expressed here could be crucial to the positive effects of S-MPEC on wound-healing. Part of the problem in that condition is the release of serotonin which does two main things: 1) it causes vasoconstriction (in an attempt to reduce blood loss) which S-MPEC antagonizes and 2) it causes thrombosis (again to reduce blood loss) which S-MPEC antagonizes. Good circulation for wound-healing is essential.

EXAMPLE 6

Effect of S-MPEC on the inhibition of rectal mucosa blood flow caused by serotonin (5-HT)

Experimental Method

SD strain male rats (b.w. 388 - 588g) were fixed in dorsal position under pentobarbital-Na (45mg/kg,i.p.) anesthesia. After the tissue of rectal

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circumference was exfoliated, the surface of mucosa was made to crop out and fixed on cork board with pin. Cannulae were put on to the right femoral vein and the total carotid artery for 5-HT administration and hemodynamometry, respectively and the probe of laser doppler flowmeter (PeriFlux, Sweden) was attached to the rectal mucosa. S-MPEC suspended in 0.5% Tween 80 was given in rectum after having identified that blood pressure became stable. Ten $\mu\text{g/kg}$ of 5-HT was injected 15 min. after S-MPEC administration. Mucosa blood flow was measured 5 min. and 1 min. after 5-HT injection. Test results are tabulated as follows:

Table 8

| | 5-HT ALONE | 5-HT+S-MPEC | % ANTAGONISM |
|---|------------|-------------|-----------------|
| Reduction in blood pressure (mm. Hg.) | 60 | 60 | 0 |
| Reduction in rectal mucosal blood-flow - Flow meter output (volts) | 3.9 | 1.3 | 67 |

These results show that S-MPEC antagonizes the effect of 5-HT in decreasing rectal mucosal blood flow in rats (5 HT_2 receptor), but does not antagonize the blood pressure-lowering effects of 5HT on arterial blood pressure (5HT₁ receptor).

The following examples illustrate formulations containing pure S-MPEC, optionally admixed with up to about 10%, preferably below about 4%, of R-MPEC, suitable for treating animals, especially humans, in need of a 5HT₂ receptor blocking effect.

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EXAMPLE 7

Topical or Hemorrhoidal Cream

The base of the cream contains:

| | | |
|---|-------------------|---------|
| | Petrolatum Album | 71.0 gm |
| 5 | Liquid petrolatum | 25.0 gm |
| | White Beeswax | 3.0 gm |
| | Water | 1.0 gm |

| | |
|-------|----------|
| Total | 100.0 gm |
|-------|----------|

- 10 The base is prepared by triturating all the ingredients together until homogenous.

Active Cream:

| | | |
|----|------------|----------|
| | S - MPEC | 1.0 gm |
| | Base Cream | 99.0 gm |
| 15 | Total | 100.0 gm |

Stability of MPEC in Base Cream (Active Cream)

- 20 The stability of the active cream was examined by storing samples of the cream at room temperature (24-27°C.), 50°C. and 80°C. and under intense fluorescent light for 6 and 12 weeks, and assaying the percentage of the initial S-MPEC remaining after the indicated storage time.

The results are shown in the following table:

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Table 9

| Condition | Time | Assay |
|-------------------|----------|-------|
| | 0 | 101.0 |
| Room Temp. | 12 weeks | 100.0 |
| | | 101.1 |
| 50°C. | 6 weeks | 100.3 |
| | | 100.9 |
| | 12 weeks | 99.9 |
| | | 100.4 |
| 80°C. | 6 weeks | 99.9 |
| | | 100.2 |
| | 12 weeks | 100.3 |
| | | 101.1 |
| Fluorescent light | 6 weeks | 98.0 |
| | | 99.3 |
| | 12 weeks | 97.8 |
| | | 96.5 |

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EXAMPLE 8 - Tablet

| <u>Material</u> | <u>Amount</u> |
|----------------------------|---------------|
| S-MPEC | 50.0 g. |
| Magnesium stearate | 1.3 g. |
| 5 Corn starch | 12.4 g. |
| Corn starch pregelatinized | 1.3 g. |
| Lactose | 185.0 g. |

The foregoing materials are blended in a twin-shell blender and then granulated and pressed into tablets weighing 250 mg. each. Each tablet contains 50
10 milligrams of active ingredient. The tablet may be scored in quarters so that a dose of 12.5 mg. of active ingredient may be conveniently obtained.

EXAMPLE 9 - Capsule

| <u>Materials</u> | <u>Amount</u> |
|--------------------|---------------|
| S-MPEC | 125 g. |
| 15 Lactose | 146.0 g. |
| Magnesium Stearate | 4.0 g. |

The foregoing materials are blended in a twin-shell blender and then filled into No. 1 hard gelatin capsules so that each capsule contains 12.5 mg. of
20 active ingredient.

EXAMPLE 10 - Intravenous Solution

A sterile solution is prepared by dissolving 10.0 g. of S-MPEC in a minimal amount of 0.5 N hydrochloric acid. This solution is adjusted to a pH of 4.3 with 0.1N sodium hydroxide and diluted to 1,000 ml. total volume with saline.
25 The solution is sterilized by passage through a bacteriological filter.

This invention has been disclosed with respect to certain preferred embodiments, and it will be understood that modifications and variations thereof obvious to those skilled in the art are to be included within the spirit and purview of

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this application and the scope of the appended claims.

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C L A I M S

1. Compounds or mixtures thereof selected from the group consisting of R-isomer-free S-2'- [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide (S - MPEC), a pharmaceutically acceptable acid salt thereof, and any mixtures thereof with up to
5 about 10% of any of their corresponding R-isomers (R-MPEC) and salts thereof.
2. Mixtures according to claim 1, containing about 0.1% to about 4% of the R isomer.
3. Compounds and mixtures thereof according to claim 1, containing the hydrochloride salt of S-MPEC.
- 10 4. S-MPEC entirely or substantially free of R-MPEC.
5. S-[2-(o-aminophenethyl)-1-methylpiperidine-dibenzoyl-L-tartrate salt] S-APEMP.DBLT.
6. A method of preparing the intermediate compound of claim 5, comprising reacting 1 mol of 2-nitrobenzaldehyde with 1 mol of
15 2-picoline in the presence of acetic anhydride and treating the resulting 2-(o-nitrostyryl)-pyridine with a quartermizing methylating agent to produce the corresponding 2-(o-nitrostyryl)-1-methylpyridinium salt, reducing the pyridinium salt by catalytic hydrogenation to produce the corresponding 2-(o-aminophenethyl)-1-methylpiperidine (RS-APEMP) hydro salt, treating the hydro salt with an alkaline
20 agent to liberate the free base (RS-APEMP) and treating the free base with dibenzoyl-L-tartaric acid to produce S-APEMP-DBLT.
7. A method according to claim 6, followed by liberating the S-APEMP free base from its DBLT salt by treatment with an alkaline agent and reacting the S-APEMP with an equimolar amount of cinnamoyl chloride to produce
25 S-MPEC.
8. A therapeutic composition comprising a pharmaceutical carrier containing as an active ingredient an effective 5HT₂ receptor blocking amount of a compound or mixture as defined in any one of claims 1 to 4.
9. A composition according to claim 8, in the form of a paste, ointment,
30 cream or gel suitable for topical application wherein said vehicle comprises a gelling, binding or thickening agent to provide the desired viscosity.
10. A composition according to claim 8, in the form of a tablet, capsule,

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chewing gum, lozenge, powder, aerosol, spray, suppository, enema, syrup, elixir, aqueous or oily suspension, emulsion, or solution, paste, ointment, cream or gel suitable for systemic oral, rectal or parenteral administration as by subcutaneous, intraperitoneal, intramuscular or intravenous injection or transdermal or inhalation therapy.

11. A method for treating an animal in need of a 5HT₂ receptor blocking effect comprising administering to said animal a therapeutically effective 5HT₂ receptor blocking amount of a compound or mixture as defined in any one of claims 1 to 4.

12. A method according to claim 11, for treating or preventing hemorrhoids, varicose veins, or venous or coronary insufficiency, or treating wounds, or providing analgesic or local anesthetic effects in such animals.

13. A method of treating an animal in need of a 5HT₂ receptor blocking effect comprising administering to said animal a therapeutically effective 5HT₂ receptor blocking amount of a composition as defined in claim 8.

14. A method according to claim 13, for treating or preventing hemorrhoids, varicose veins, or venous or coronary insufficiency, or treating wounds, in such animal.

15. The method of claim 11, wherein said animal is a human.

16. The method of claim 12, wherein said animal is a human.

17. The method of claim 13, wherein said animal is a human.

18. The method of claim 14, wherein said animal is a human.

19. S-MPEC produced by the method of claim 7.

20. Use of a compound or mixture as defined in any one of claims 1 to 4, for the manufacture of a medicament for treating an animal in need of a 5-HT₂ receptor blocking effect.

21. Use of a compound or mixture as defined in any one of claims 1 to 4, for the manufacture of a medicament for an animal for treating or preventing hemorrhoids, varicose veins or venous or coronary insufficiency or treating wounds or providing analgesic or local anesthetic effects.

22. The use of claim 20, wherein said animal is a human.

23. The use of claim 21, wherein said animal is a human.

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24. A medicine for treating a 5-HT₂ receptor blocking effect characterized in that the medicine comprised a therapeutically acceptable amount of a compound or mixture as defined in any one of claims 1 to 4.

25. A medicine according to claim 24, for treating or preventing
5 hemorrhoids, varicose veins, or venous or coronary insufficiency or treating wounds or providing analgesic or local anesthetic effects.

AMENDED CLAIMS

[received by the International Bureau on 15 June 1998 (15.06.98);
original claims 1 - 25 replaced by new claims 1 - 17 (2 pages)]

1. A therapeutic composition comprising a pharmaceutical carrier containing as an active ingredient an effective 5-HT₂ receptor blocking amount of a compound selected from R-isomer-free S-2'- [2-(1-methyl-2-piperidyl) ethyl] cinnamanilide (S - MPEC), a pharmaceutically acceptable acid salt thereof, and any mixtures thereof with up to about 10% of any of their corresponding R-isomers (R-MPEC) and salts thereof.
2. A composition according to claim 1, containing about 0.1% to about 4% of the R isomer.
3. A composition according to claim 1 or 2, containing S-MPEC or its HCl salt entirely or substantially free of R-MPEC.
4. A composition according to any one of claims 1, 2 or 3, in the form of a paste, ointment, cream or gel suitable for topical application wherein said vehicle comprises a gelling, binding or thickening agent to provide a predetermined viscosity.
5. A composition according to any one of claims 1, 2 or 3, in the form of a tablet, capsule, chewing gum, lozenge, powder, aerosol, spray, suppository, enema, syrup, elixir, aqueous or oily suspension, emulsion, or solution, paste, ointment, cream or gel suitable for systemic oral, rectal or parenteral administration as by subcutaneous, intraperitoneal, intramuscular or intravenous injection or transdermal or inhalation therapy.
6. S-[2-(o-aminophenethyl)-1-methylpiperidine-dibenzoyl-L-tartrate salt] (S-APEMP.DBLT).
7. A method of preparing the compound of claim 6, comprising reacting 1 mol of 2-nitrobenzaldehyde with 1 mol of 2-picoline in the presence of acetic anhydride and treating the resulting 2-(o-nitrostyryl)-pyridine with a quarternizing methylating agent to produce the corresponding 2-(o-nitrostyryl)-1-methylpyridinium salt, reducing the pyridinium salt by catalytic hydrogenation to produce the corresponding 2-(o-aminophenethyl)-1-methylpiperidine (RS-APEMP) hydro salt, treating the hydro salt with an alkaline agent to liberate the free base (RS-APEMP) and treating the free base with dibenzoyl-L-tartaric acid to produce S-APEMP-DBLT.
8. A method according to claim 7, followed by liberating the

free base from its DBLT salt by treatment with an alkaline agent and reacting the S-APEMP with an equimolar amount of cinnamoyl chloride to produce S-MPEC.

9. A medicine to obtain a 5-HT₂ receptor blocking effect characterized in that the medicine comprises a therapeutically acceptable amount of a composition as defined in any one of claims 1, 2 or 3.
10. A medicine according to claim 9, for treating or preventing hemorrhoids, varicose veins, or venous or coronary insufficiency or treating wounds or providing analgesic or local anesthetic effects.
11. A method for treating an animal in need of a 5-HT₂ receptor blocking effect comprising administering to said animal a therapeutically effective 5-HT₂ receptor blocking amount of a composition as defined in any one of claims 1, 2 or 3.
12. A method according to claim 11, for treating or preventing hemorrhoids, varicose veins, or venous or coronary insufficiency, or treating wounds, or providing analgesic or local anesthetic effects in such animals.
13. The method of claim 11 or 12, wherein said animal is a human.
14. S-MPEC produced by the method of claim 8.
15. Use of a composition as defined in any one of claims 1, 2, or 3, for the manufacture of a medicament for treating an animal in need of a 5-HT₂ receptor blocking effect.
16. Use of a composition as defined in any one of claims 1, 2, or 3, for the manufacture of a medicament for an animal for treating or preventing hemorrhoids, varicose veins or venous or coronary insufficiency or treating wounds or providing analgesic or local anesthetic effects.
17. The use of claim 15 or 16, wherein said animal is a human.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/01304

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D211/26 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | US 4 064 254 A (DYKSTRA STANLEY J ET AL) 20 December 1977 cited in the application see example 141 | 1-4, 8-25 |
| Y | see example 141A | 5-7 |
| X | WO 94 18958 A (SAM AMER & CO INC ; AMER M SAMIR (US)) 1 September 1994 cited in the application see compound I see page 11 | 8-25 |
| Y | WO 95 21819 A (MERCK SHARP & DOHME ; BAKER RAYMOND (GB); MACLEOD ANGUS MURRAY (GB)) 17 August 1995 see page 10, line 29 - line 30 see page 28, line 23 - line 33 | 5-7 |
| | -/-- | |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 April 1998

Date of mailing of the international search report

20.04.98

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/01304

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| Y | <p>PORTOGHESE, PHILIP S. ET AL: "Stereochemical studies on medicinal agents. 13. Correlation of the solid-state conformations of 1,3,5-trimethyl- and 1,3-dimethyl-4-phenyl-4-propionoxypiperidi ne enantiomers with their absolute stereoselectivity at analgetic receptors" J. MED. CHEM. (1973), 16(3), 199-203 CODEN: JMCMAR, 1973, XP002061306 see optical resolution of compound 5 -----</p> | - 5-7 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 01304

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 11-18
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int .ional Application No

PCT/US 98/01304

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